

Amendments to the Claim:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) An isolated polynucleotide encoding a mosquito deoxyribonucleoside kinase derived from a yellow fever mosquito, said isolated polynucleotide being selected from the group consisting of:

- ~~a. an isolated polynucleotide encoding multisubstrate deoxyribonucleoside kinase derived from yellow fever mosquito *Aedes aegypti*,~~
- ~~b. an isolated polynucleotide having the nucleotide sequence of SEQ ID No. 1,~~
- ~~c. an isolated polynucleotide encoding a polypeptide having the sequence of SEQ ID No. 2,~~
- ~~d. an isolated polynucleotide encoding a multisubstrate deoxyribonucleoside kinase, wherein said polynucleotide has at least 70% sequence identity to SEQ ID No. 1,~~
- a.e. an isolated polynucleotide encoding a multisubstrate deoxyribonucleoside kinase having at least 80% amino acid sequence identity to SEQ ID No. 2 when percentage identity is determined over the entire length of SEQ ID NO:2,
- ~~f. an isolated polynucleotide capable of hybridising to the complement of a polynucleotide having the nucleotide sequence of SEQ ID No. 1, said isolated polynucleotide encoding a multisubstrate deoxyribonucleoside kinase, and~~
- ~~b.g. the complement of any of a through f.~~

2. (Previously Presented) The polynucleotide of claim 1, encoding a deoxyribonucleoside kinase enzyme derived from a *Aedes aegypti*, which kinase enzyme, when compared to human *Herpes*

*simplex* virus 1 (HSV-TK1) and upon transformation into an eukaryotic cell, decreases at least four (4) fold the IC<sub>50</sub> of at least one nucleoside analogue.

3. (Previously Presented) The polynucleotide of claim 1, encoding a deoxyribonucleoside kinase variant derived from mosquito, which deoxyribonucleoside kinase enzyme variant, when compared to human *Herpes simplex* virus 1 (HSV-TK1) and upon transformation into an eukaryotic cell, decreases at least four (4) fold the IC<sub>50</sub> of at least one nucleoside analogue.

4. (Currently Amended) The polynucleotide of claim 1, wherein the isolated polynucleotide ~~has~~ comprises the nucleotide sequence of SEQ ID No. 1.

5. (Currently Amended) The polynucleotide of claim 1, wherein the isolated polynucleotide encodes a polypeptide ~~having~~ comprising the sequence of SEQ ID No. 2.

6. (Original) The polynucleotide of claim 1, wherein the isolated polynucleotide is capable of hybridising to the complement of a polynucleotide having the nucleotide sequence of SEQ ID No. 1, said isolated polynucleotide encoding a multisubstrate deoxyribonucleoside kinase.

7. (Currently Amended) The isolated polynucleotide of claim 1, which ~~has~~ comprises a polynucleotide sequence having at least 73% 85% nucleotide sequence identity to the polynucleotide sequence presented as SEQ ID NO: 1 when determined over its the entire length of SEQ ID NO:1.

8. (Cancelled)

9. (Original) The isolated polynucleotide of claim 1, encoding a C-terminally truncated multisubstrate deoxyribonucleoside kinase.

10. (Withdrawn - Currently Amended) An isolated ~~mosquito~~ deoxyribonucleoside kinase enzyme ~~selected from the group consisting of:~~

a. ~~an isolated mosquito deoxyribonucleoside kinase enzyme encoded by the polynucleotide of claim 1,~~

b. ~~an isolated mosquito deoxyribonucleoside kinase enzyme~~

~~derived from from yellow fever mosquito *Aedes aegypti*,  
c. a polypeptide having the sequence of SEQ ID No. 2, and  
d. a multisubstrate deoxyribonucleoside kinase having at  
least 80% sequence identity to SEQ ID No. 2.~~

11. (Withdrawn - Currently Amended) The isolated multisubstrate deoxyribonucleoside kinase of claim 7 10, being derived from yellow fever mosquito *Aedes aegypti*.

12. (Withdrawn) The isolated deoxyribonucleoside kinase of claim 10, which multisubstrate deoxyribonucleoside kinase enzyme, when expressed and compared to human *Herpes simplex* virus 1 (HSV-TK1) and upon transduction into a eukaryotic cell, decreases at least four (4) fold the IC<sub>50</sub> of at least one nucleoside analogue.

13. (Withdrawn - Currently Amended) The ~~mosquito~~ deoxyribonucleoside kinase of claim 10, comprising the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence of at least 85% identity with this sequence, when determined over its entire length.

14. (Withdrawn - Currently Amended) The ~~mosquito~~ deoxyribonucleoside kinase of claim 10 comprising the amino acid sequence of SEQ ID NO: 2, ~~or a functional analogue thereof.~~

15. (Withdrawn - Currently Amended) The ~~mosquito~~ deoxyribonucleoside kinase of claim 10, which decreases at least three (3) fold the lethal dose (LD<sub>100</sub>) of at least one nucleoside analogue when compared to the action of a thymidine kinase derived from human *Herpes simplex* virus 1 (HSV-TK1).

16. (Previously Presented) A vector construct comprising the polynucleotide of claim 1, and a promoter operably linked to the polynucleotide.

17. (Withdrawn - Currently Amended) The vector construct of claim 16 which is being a viral vector, ~~in particular a *Herpes simplex* viral vector, an adenoviral vector, an adenovirus-associated viral vector, a lentivirus vector, a retroviral vector or a vacciniaviral vector.~~

18. (Withdrawn) A packaging cell line capable of producing an infective virion comprising the vector of claim 16.

19. (Previously Presented) An isolated host cell genetically modified with the polynucleotide of claim 1.

20. (Currently Amended) The host cell of claim 19, which is a eukaryotic cell ~~such as a human cell~~.

21. (Withdrawn - Currently Amended) The host cell of claim 20, being selected from the group consisting of human stem cells, ~~and human precursor cells, such as human neural stem or precursor cells~~.

22. (Currently Amended) The host cell of claim 19, which is a prokaryotic cell ~~such as a bacterial cell, such as E. coli~~.

23-25. (Cancelled)

26. (Withdrawn - Currently Amended) An article ~~containing~~ comprising a nucleoside analogue and a source of an *Aedes aegypti* derived deoxyribonucleoside kinase for the simultaneous, separate or successive administration in cancer therapy.

27. (Withdrawn) Article according to claim 26, wherein the nucleoside analogue is a cytidine analogue.

28. (Withdrawn) Article according to claim 26, wherein the nucleoside analogue is Gemcitabine or AraC.

29. (Withdrawn - Currently Amended) Article ~~containing~~ comprising a nucleoside analogue and a source of ~~an Aedes aegypti derived~~ a deoxyribonucleoside kinase for the simultaneous, separate or successive administration in cancer therapy, wherein the source of deoxyribonucleoside kinase comprises the nucleotide sequence of claim 1.

30. (Withdrawn - Currently Amended) Article ~~containing~~ comprising a nucleoside analogue and a source of ~~an Aedes aegypti derived~~ a deoxyribonucleoside kinase for the simultaneous, separate or successive administration in cancer therapy, wherein the source of deoxyribonucleoside kinase comprises the polypeptide of claim 10.

31. (Withdrawn - Currently Amended) Article ~~containing~~ comprising a nucleoside analogue and a source of a ~~an Aedes~~

~~aegypti-derived~~ deoxyribonucleoside kinase for the simultaneous, separate or successive administration in cancer therapy, wherein the source of deoxyribonucleoside kinase comprises the host cell of claim 19.

32. (Withdrawn - Currently Amended) Article ~~containing~~ comprising a nucleoside analogue and a source of a ~~an Aedes aegypti-derived~~ deoxyribonucleoside kinase for the simultaneous, separate or successive administration in cancer therapy, wherein the source of deoxyribonucleoside kinase comprises the packaging cell line of claim 18.

33. (Withdrawn) A method of sensitising a cell to a nucleoside analogue prodrug, which method comprises the steps of  
(i) transfecting or transducing said cell with a polynucleotide sequence according to claim 1 encoding a deoxyribonucleoside kinase enzyme, that promotes the conversion of said prodrug into a (cytotoxic) drug; and  
(ii) delivering said nucleoside analogue prodrug to said cell;

wherein said cell is more sensitive to said (cytotoxic) drug than to said nucleoside analogue prodrug.

34. (Withdrawn) The method of claim 33, wherein the nucleoside analogue is a cytidine analogue.

35. (Withdrawn) The method of claim 33, wherein the nucleoside analogue is gemcitabine (dFdC) or AraC.

36. (Withdrawn) A method of inhibiting a pathogenic agent in a warm-blooded animal, which method comprises administering to said animal a polynucleotide of claim 1.

37. (Withdrawn) The method of claim 36, wherein said polynucleotide sequence or said vector is administered *in vivo*.

38. (Withdrawn) The method of claim 36, wherein said pathogenic agent is a virus, a bacteria or a parasite.

39. (Withdrawn - Currently Amended) The method of claim 36, wherein said pathogenic agent is a ~~tumour~~ tumor cell.

40. (Withdrawn) The method of claim 36, wherein said

pathogenic agent is an autoreactive immune cell.

41. (Withdrawn) The method of claim 36, further comprising the step of administering a nucleoside analogue to said warm-blooded animal.

42. (Withdrawn) The method of claim 41, wherein said nucleoside analogue is a cytidine analogue.

43. (Withdrawn - Currently Amended) The method of claim 41, wherein said nucleoside analogue is gemcitabine (dFdC), or AraC, ~~preferably gemcitabine.~~

44-45. (Cancelled)

46. (Withdrawn - Currently Amended) A method of phosphorylating a nucleoside or a nucleoside analog, comprising the steps of

- i) subjecting the nucleoside or nucleoside analog to the action of the ~~mosquito~~ deoxyribonucleoside kinase enzyme of claim 10, and
- ii) recovering the phosphorylated nucleoside or nucleoside analog.

47. (Withdrawn) The method of claim 46, wherein the nucleoside or nucleoside analog is a purine.

48. (Withdrawn - Currently Amended) A method of non-invasive nuclear imaging of transgene expression of a ~~mosquito~~ deoxyribonucleoside kinase enzyme ~~of the invention~~ in a cell or subject, which method comprises the steps of

- (i) transfecting or transducing said cell or subject with a polynucleotide sequence encoding the ~~mosquito~~ deoxyribonucleoside kinase enzyme of claim 10, which enzyme promotes the conversion of a substrate into a substrate-monophosphate;
- (ii) delivering said substrate to said cell or subject; and
- (iii) non-invasively monitoring the change to said prodrug in said cell or subject.

49. (Withdrawn - Currently Amended) The method of claim 48, wherein the monitoring carried out in step (iii) is performed by Single Photon Emission Computed Tomography (SPECT), by Positron Emission Tomography (PET), by Magnetic Resonance Spectroscopy (MRS), by Magnetic Resonance Imaging (MRI), or by Computed Axial X-ray Tomography (CAT), or a combination thereof.

50. (Withdrawn) The method of claim 48, wherein the substrate is a labelled nucleoside analogue.

51-54. (Cancelled)

55. (Previously Presented) A method of preparing the deoxyribonucleoside kinase enzyme of claim 10 comprising culturing a host cell genetically modified with a polynucleoside encoding said enzyme in expressible form and recovering the enzyme from the culture medium and/or the cells.

56. (New) The polynucleotide of claim 1 wherein said polypeptide comprises an amino acid sequence which has at least 90% identity to SEQ ID NO:2.

57. (New) The polynucleotide of claim 1 wherein said polypeptide comprises an amino acid sequence which has at least 95% identity to SEQ ID NO:2.

58. (New) The polynucleotide of claim 1 wherein said polypeptide comprises an amino acid sequence which has at least 98% identity to SEQ ID NO:2.

59. (New) The polynucleotide of claim 1 wherein the polypeptide comprises an amino acid sequence which differs from SEQ ID NO:2 solely by amino acid replacement at the semi-conserved or non-conserved positions identified in Figure 1.

60. (New) The polynucleotide of claim 59 wherein each replaced amino acid of SEQ ID NO:2 is replaced with an amino acid which appears at corresponding aligned position in another insect kinase.

61. (New) The polynucleotide of claim 1 wherein the polypeptide comprises an amino acid sequence which differs from SEQ ID NO:2 solely by amino acid replacement at the non-conserved positions identified in Figure 1.

62. (New) The polynucleotide of claim 61 wherein each replaced amino acid of SEQ ID NO:2 is replaced with an amino acid which appears at corresponding aligned position in another insect kinase.

63. (New) The polynucleotide of claim 1 wherein the polypeptide comprises an amino acid sequence which differs from SEQ ID NO:2 solely by one or more of the following substitutions:

- (i) substitution of an amino acid selected from the group consisting of Ala, Leu, Ile, Val, Pro, Met, Phe and Trp for another of that group,
- (ii) the substitution of an amino acid selected from the group consisting of Ser, Thr, Tyr, Asn, Gln and Cys for another of that group,
- (iii) the substitution of an amino acid selected from the group consisting of Lys, Arg and His for another of that group, and
- (iv) the substitution of Asp for Glu or vice versa.

64. (New) The polynucleotide of claim 1 wherein said polypeptide is characterized by an amino acid sequence identical to SEQ ID NO:2.

65. (New) An isolated polynucleotide encoding a mosquito deoxyribonucleoside kinase derived from a yellow fever mosquito, said isolated polynucleotide being:

- c) an isolated polynucleotide capable of hybridizing to the complement of a polynucleotide having the nucleotide sequence of SEQ ID No. 1, said isolated polynucleotide encoding a multisubstrate deoxyribonucleoside kinase,
- under medium stringency conditions, or d) a complement thereof.

66. (New) The polynucleotide of claim 65 wherein the hybridization occurs under conditions of medium/high stringency.

67. (New) The polynucleotide of claim 65 wherein the hybridization occurs under conditions of high stringency.

68. (New) The polynucleotide of claim 65 wherein the



hybridization occurs under conditions of very high stringency.

69. (New) The polynucleotide of claim 7 which comprises a polynucleotide sequence having at least 90% nucleotide sequence identity to SEQ ID NO:1.

70. (New) The polynucleotide of claim 7 which comprises a polynucleotide sequence having at least 95% nucleotide sequence identity to SEQ ID NO:1.

71. (New) The polynucleotide of claim 7 which comprises a polynucleotide sequence having at least 98% nucleotide sequence identity to SEQ ID NO:1.

72. (New) The polynucleotide of claim 7 which is identical to SEQ ID NO:1.